The Importance of Critically Analyzing Assumptions in Pharmacoeconomic Models: A Case Study in Modeling a Comparison of Diabetes Treatments

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Background

- On June 30, 2014, the *Journal of the American Medical Association Internal Medicine* (JAMA Internal Medicine) published online “Effect of Patients’ Risks and Preferences on Health Gains With Plasma Glucose Level Lowering in Type 2 Diabetes Mellitus” by Vijan et al.¹

- Article conclusion was thought provoking and potentially clinical-practice changing²:

  “*for most patients older than 50 years with an HbA1c level less than 9% receiving metformin therapy, additional glycemic treatment usually offers at most modest benefits.*”

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2. *JAMA Internal Medicine* is a highly influential journal, impact factor of 16.54, ranking 2nd among internal medicine journals, 6th among 156 general medical journals (https://jamanetwork.com/journals/jamainternalmedicine/pages/for-authors/)
Background

- Vijan et al. estimated the effects of hemoglobin A1c (HbA1c) reduction on diabetes clinical outcomes and overall quality-adjusted life years (QALYs) using a Markov simulation model.
- Performed an intensive examination of the Vijan model, resulted in a number of questions related to assumptions, questions that could not be answered from the information provided in the article, its supplemental material, or the cited publications.
- Assumptions in question greatly influence the results and subsequent conclusions, and thus merit greater transparency.
Background

- Vijan et al. model compared two interventions:
  - “Initiation of metformin therapy at diagnosis”
  - “Switch to insulin” scenario, the patients’ HbA1c levels were assumed to have increased to 8.5% (presumably from 7.0%) over ten years
Background

- Serious questions about assumptions underlying modeling of each intervention
  - “Initiation of metformin therapy at diagnosis”
    - Model did not account for possibility of metformin failure
    - Patients not taking basal-bolus insulin have a demonstrated HbA1c drift over time, shown in multiple studies.\(^3,4,5,6,7\)

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Background – Metformin HbA1c drift

Background

• Serious questions about assumptions underlying modeling of each intervention
  o “Switch to insulin”
    ▪ Patients’ HbA1c levels were assumed to have increased to 8.5% (presumably from 7.0%) over ten years
    ▪ Delay in treatment and time spent in poor glycemic control is a critically important determinant of patient outcomes\(^8\)
    ▪ Ten-year period of uncontrolled HbA1c levels increase the patients’ risks of diabetes complications
      ▪ Disutility from these increased complications incorrectly attributed by the model to the “insulin” scenario when in fact these are due to the failure of metformin to sustain glycemic control

Objective

• To examine the clinical and humanistic effects of incorporating HbA1c drift in a type 2 diabetes pharmacoeconomic model
Methods

• Monte Carlo microsimulation model to estimate diabetes-related complications and mortality under various treatment strategies for newly-diagnosed patients with Type 2 diabetes mellitus (T2DM)
• Model is referred to as the Treatment Transitions Model (TTM)
• TTM is an adaptation of the United Kingdom Prospective Diabetes Study (UKPDS) Outcomes Model 2, commonly referred to as “UKPDS 82”

Methods

**TTM Flow**

1. Start
2. Create individual patient and assign baseline characteristics (incl HbA1c level)
3. Determine if patient experiences a major T2DM complication event(s)
4. If yes, End; if no, Update patient HbA1c level
5. If yes, Did patient die this model cycle?
   - Yes: End
   - No: Last model cycle?
     - Yes: End
     - No: Update treatment (within the strategy)

**Diagram**

- Start
- Create individual patient and assign baseline characteristics (incl HbA1c level)
- Determine if patient experiences a major T2DM complication event(s)
- Did patient die this model cycle?
  - Yes: End
  - No: Last model cycle?
    - Yes: End
    - No: Update treatment (within the strategy)
    - No: Update patient HbA1c level
      - No: Determine if patient experiences a major T2DM complication event(s)
        - Yes: End
        - No: Last model cycle?
Methods

• Underlying TTM are 17 multivariate regression equations estimating the probability of T2DM-related macrovascular and microvascular complications, and mortality

• Mean of 11 covariates per equation
## Methods – Covariates

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGE DIAG</td>
<td>Age in years at diagnosis of diabetes</td>
</tr>
<tr>
<td>CURR AGE</td>
<td>Current age in years</td>
</tr>
<tr>
<td>YEAR</td>
<td>Duration of diabetes (years)</td>
</tr>
<tr>
<td>FEMALE</td>
<td>1 for female; 0 for male</td>
</tr>
<tr>
<td>AFRO</td>
<td>1 Afro-Caribbean ethnicity; 0 otherwise</td>
</tr>
<tr>
<td>INDIAN</td>
<td>1 for Asian Indian ethnicity; 0 otherwise</td>
</tr>
<tr>
<td>SMOKER</td>
<td>1 for current smoker; 0 otherwise</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index (m/kg(^2))</td>
</tr>
<tr>
<td>BMI CAT1</td>
<td>Body mass index &lt; 18.5m/kg(^2)</td>
</tr>
<tr>
<td>BMI CAT3</td>
<td>Body mass index &gt; 25m/kg(^2)</td>
</tr>
<tr>
<td>HbA1C</td>
<td>HbA1c (%)</td>
</tr>
<tr>
<td>SBP</td>
<td>Systolic blood pressure (mm Hg)</td>
</tr>
<tr>
<td>HDL</td>
<td>High density lipoprotein cholesterol (mmol/l)</td>
</tr>
<tr>
<td>LDL</td>
<td>Low density lipoprotein cholesterol (mmol/l)</td>
</tr>
<tr>
<td>LDL&gt;35</td>
<td>Low density lipoprotein cholesterol (mmol/l)</td>
</tr>
<tr>
<td>HEART R</td>
<td>Heart rate (beats per minute)</td>
</tr>
<tr>
<td>eGFR</td>
<td>Estimated glomerular filtration rate</td>
</tr>
<tr>
<td>eGFR&lt;60</td>
<td>Estimated glomerular filtration rate</td>
</tr>
<tr>
<td>eGFR&gt;60</td>
<td>Estimated glomerular filtration rate</td>
</tr>
<tr>
<td>MIC ALB</td>
<td>Presence of micro- or macro-albuminuria</td>
</tr>
<tr>
<td>PVD</td>
<td>1 for peripheral vascular disease; 0 otherwise</td>
</tr>
<tr>
<td>WBC</td>
<td>White blood cell count</td>
</tr>
<tr>
<td>HAEM</td>
<td>Haemoglobin g/dL</td>
</tr>
<tr>
<td>AMP EVENT</td>
<td>1 for first amputation; 0 otherwise</td>
</tr>
<tr>
<td>AMP2 EVENT</td>
<td>1 for second amputation; 0 otherwise</td>
</tr>
<tr>
<td>AMP HIST</td>
<td>1 for history of amputation; 0 otherwise</td>
</tr>
</tbody>
</table>
Methods

Macrovascular complications, functional form of risk equation

• 1\textsuperscript{st} congestive heart failure, Weibull
• 1\textsuperscript{st} ischaemic heart disease, Weibull
• 1\textsuperscript{st} myocardial infarction (male), Exponential
• 1\textsuperscript{st} myocardial infarction (female), Weibull
• 2\textsuperscript{nd} myocardial infarction, Exponential
• 1\textsuperscript{st} stroke, Weibull
• 2\textsuperscript{nd} stroke, Weibull
Methods

Microvascular complications, functional form of risk equation

- Blindness, Exponential
- Ulcer, Logistic
- 1st amputation no prior ulcer, Weibull
- 1st amputation no prior ulcer, Exponential
- 2nd amputation, Exponential
- Renal failure, Exponential
Methods

Microvascular complications, functional form of risk equation

• Death in years with no history or events, Gompertz
• Death in 1st year of event(s), Logistic
• Death in years with history but not events, Gompertz
• Death in subsequent year/s of event(s), Logistic
Methods – Example risk eq. calculation

Annual probability of congestive heart failure (CHF), functional form is Weibull
Baseline hazard

\[ h_0(t) = \rho t^{\rho-1} \exp(\lambda) \]

Proportional hazards model

\[ h(t|x_j) = h_0(t) \exp(\beta_j x_j) = \rho t^{\rho-1} \exp(\lambda + \beta_j x_j) \]

Integrated hazard at time \( t \)

\[ H(t|x_j) = \exp(\lambda + \beta_j x_j)t^\rho \]

Unconditional probability of CHF in the interval \( t \) to \( t + 1 \)

\[ 1 - \exp\{H(t|x_j) - H(t + 1|x_j)\} \]
Methods – Example risk equation calculation

Calculation of probability of CHF in current year
Male, 70 years of age, 8-year history of diabetes, LDL 3.0 mmol/l, BMI of 32, eGFR 50, with microalbuminuria and a history of amputation
Methods – Example risk eq. calculation

\[ t = 8 \text{ years of diabetes} \]

\[
H(t \mid x_j) = \exp(-12.332 + 0.068 \times 62 + 3 \times 10 \times 0.012 + 0.072 \times 32 + (50/10) \times -0.22 + 0.771 + 0.658) \times 8^{1.514}
\]

\[ = 0.1388 \]

\[ t + 1 = 9 \text{ years of diabetes} \]

\[
H(t + 1 \mid x_j) = \exp(-12.332 + 0.068 \times 62 + 3 \times 10 \times 0.012 + 0.072 \times 32 + (50/10) \times -0.22 + 0.771 + 0.658) \times 9^{1.514}
\]

\[ = 0.1659 \]

Probability of CHF in current year

\[ = 1 - \exp(0.1388 - 0.1659) = 0.027 \]
Methods-scenario runs

- T2DM patient baseline characteristics based on NHANES data: mean age 62, mean HbA1c 7.5
- Time frame: lifetime
- Base case: no treatment
- Comparator 1: metformin treatment without drift
- Comparator 2: metformin treatment with drift
- Comparator 3: insulin treatment
- Benefit of metformin treatment without drift, metformin treatment with drift and insulin treatment
Not considering drift according to Vijan et al.

Vijan metformin tx benefits:
- Assume HbA1c keep constant when not on tx
- In reality/clinical trials: oral antidiabetic drugs suffer from HbA1c drift
- The benefit of metformin tx is overestimated when not considering drift

Real metformin tx benefits:
- No treatment
- Metformin
Not considering drift according to Vijan et al.

Vijan metformin tx benefits:

Vijan insulin tx benefits:

- False message delivered: metformin tx is way more beneficial than insulin tx
Results – Comparing benefit of metformin without and with drift

Complications prevented with metformin treatment

benefit of metformin (no drift) over no tx vs benefit of metformin (with drift) over no tx
Results – Comparing benefit of metformin without drift, with drift, and insulin

Complications prevented with metformin or insulin treatment

Benefit of insulin tx is larger than benefit of “real” metformin but is similar to benefit of the no-drift metformin
Results – Life years gain and QALY gain with metformin treatment

LY/QALY gain of metformin (no drift) over no tx vs LY/QALY gain of metformin (with drift) over no tx
Results – Life years gain and QALY gain with metformin or insulin treatment

- LY/QALY gain of insulin tx is larger than LY/QALY gain of “real” metformin but is similar to LY/QALY gain of the no-drift metformin
Conclusion

• Incorporating HbA1c drift, insulin is superior to metformin in:
  o Preventing myocardial infarctions, stroke, blindness, ulcers of the lower limb, and lower extremity amputation
  o Gaining life years and quality-adjusted life years (QALYs)
• Before accepting model conclusions, always investigate:
  o Fundamental model assumptions
  o Each treatment alternative assumptions